C7 to standard curve. Expression levels for the Par-4 mRNA in each sample were normalized to 18S rRNA.--

In the claims:

Please amend claim 1 to read as follows:

Claim 1. (Twice amended) A method for identifying inhibitors of neuronal degeneration comprising:

(A) (1) cotransfecting eukaryotic host cells expressing a presenilin protein (PS), with a polynucleotide encoding a prostate apoptosis response-4 (Par-4) polypeptide, and an NF-κB dependent reporter construct, (2) exposing the cotransfected cells to a candidate molecule, (3) monitoring the ability of said candidate molecule to induce NF-κB activation, (4) comparing the level of NF-κB activation in the cells exposed to the candidate molecule to the level of NF-κB activation in at least one comparable control sample and (5) identifying an inhibitor of neuronal degeneration when the level of NF-κB activation in the exposed cells is significantly greater than the level of NF-κB activation in the comparable control sample; or

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(B) (1) transfecting eukaryotic host cells endogenously expressing prostate apoptosis response-4 (Par-4) polypeptide and a presenilin (PS) protein with nucleic acid encoding an NF-κB dependent reporter construct, (2) exposing the transfected cells to a candidate molecule, (3) monitoring the ability of said candidate molecule to induce NF-κB activation, (4) comparing the level of NF-κB activation in the cells exposed to the candidate molecule to the level of NF-κB activation in at least one comparable control sample and (5) identifying an inhibitor of neuronal degeneration when the level of NF-κB activation in the exposed cells is significantly greater than the level of NF-κB activation in the comparable control sample.--

REMARKS

Claims 1-17 and 53 are pending in this application. Claim 1 has been amended. The foregoing amendment is supported at least at page 3, lines 5-10, page 38, line 25-27, page 39, lines 7-12, page 39, lines 7-9 and lines 28-30, and page 40, line 27 to page 41, line 2 and does not add new matter.

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Objections

(1) Drawings

The Examiner noted that the two pages of Figure 15 in the instant application should be renumbered Figure 15A and Figure 15B. Proposed amendments to Figure 15 are submitted herewith for the Examiner's approval. Changes are marked in red. The specification has also been amended to refer to Figure 15A and B. Accordingly, Applicants request that the objection to the drawings be withdrawn.

(2) Specification

As suggested by the Examiner, the specification has been amended such that the use of trademarks are capitalized and generic terminology is included in all instances where the use of trademarks appear.

Rejections under 35 U.S.C. § 112. second paragraph

Claims 1-17 and 53 were rejected under 35 U.S.C. 112, second paragraph "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention."

(1) Claim 1 was rejected as "vague and indefinite for being incomplete for omitting essential steps, such omission amounting to a gap between the steps." According to the rejection, the omitted steps are: a comparison (control) step and the step that identifies inhibitors of neuronal degeneration. The current amendments to claim 1 add these steps and are believed to overcome the present rejection.

(2) Claim 1 is further rejected as "indefinite for use of the term 'a Par-4 polynucleotide.'" A person skilled in the art reading the present specification would readily understand that "Par-4," as used herein, refers to the prostate apoptosis response-4 protein. Par-4 is well known in the art and, further, is extensively described in the specification, for example at page 3, lines 5-10, page 39, lines 7-9 and lines 28-30, page 38, lines 7-12 and lines 28-30 and page 40, line 27-page 41, line 2. The specification has been amended to include the full name "prostate apoptosis response-4." Support for this amendment can be found at page 3, line 7 in the Guo et al. reference, which is incorporated in its entirety. Claim 1 has also been amended to include the

full name for Par-4. In view of this amendment, the general knowledge in the art and the specific teaching provided in the specification, Applicants submit that one of skill in the art would not be confused with other similar terms and request that the present rejection be withdrawn.

(3) Claim 2-27 and 53 were rejected as "indefinite for being dependent from the indefinite claim." As claims 18-52 have previously been canceled, the current rejection of claims 18-27 under 35 U.S.C. § 112, second paragraph is believed to be moot. Claims 2-17 and 53 are dependent on claim 1. The current amendment to claim 1, discussed above, is believed to overcome the present rejection.

All claims pending in this application are believed to be in *prima facie* condition of allowance, and an early action to that effect is respectfully solicited. Should the Examiner find that there are any further issues outstanding, she is invited to contact the undersigned attorney at the telephone number indicated below.

Although no fees are believed to be due at this time, please charge any fees, including any fees for extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: September 22, 2002 By: _____

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(415) 954-4114

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Version with markings to show changes made

In the specification:

The paragraph, beginning at page 3, line 4, has been amended as follows:

--Another protein that may play a role in the neuronal loss in Alzheimer's disease is Par-4. Prostate apoptosis response-4 (Par-4), a protein recently implicated as a mediator of prostate cancer, melanoma, and neuronal cell death, has been found to be elevated in vulnerable regions of the Alzheimer's disease brain (Guo *et al.*, Nature Med., 4:957-962 (1998)). Par-4 expression is also elevated in cultured cells expressing FAD PS1 (Gue *et al., supra*). Inhibition of Par-4 expression or function can prevent neuronal apoptotic cell death induced by β-amyloid or neurotrophic factor withdrawal. In addition, Par-4, has been found to specifically interact with the regulatory domain of atypical protein kinase C subfamily of isoenzymes (aPKCs), which dramatically inhibits their enzymatic activity (Diaz-Meco *et al.*, Cell 86:777-786 (1996)).--

The paragraph, beginning at page 10, line 8, has been amended as follows:

--Figures 15A and 15B show the nucleotide sequence of a human Par-4 promoter region and open reading frame (SEQ ID NO: 8). An intron is indicated by bold type and the Par-4 protein open reading frame is in bold and underlined.--

The paragraph beginning at page 16, line 4, has been amended as follows

--"Carrier" as used herein include pharmaceutically acceptable carriers, excipients, or stabilizers which are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically acceptable carrier is an aqueous pH buffered solution. Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic

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surfactants such as TWEEN™[,]; polyethylene glycol (PEG)[,]; and PLURONICS™ block copolymers.--

Please replace the paragraph beginning at page 17, line 17, with the following rewritten paragraph:

--Nucleic acid encoding a native human Par-4 protein is known in the art (PCT Publication WO 98/13494, GenBank Accession No: U63809), and is shown in Figure 11A (SEQ ID NO: 1). The encoded amino acid sequence (SEQ ID NO: 2) is shown in Figure 11B and the 5' untranslated region of Par-4 including a portion of the promoter sequence is shown in Figure 14 (SEQ ID NO: 7). Recently we have cloned and sequenced the entire Par-4 promoter region, which is shown in Figures 15A and 15B along with the beginning of the coding region (SEQ ID NO: 8).--

The paragraph beginning at page 18, line 24, has been amended as follows:

--At least one intron, identified in bold in Figure 15B, is located in the Par-4 promoter. This intron is located in the 5' untranslated region and was identified by comparing the gene sequence with a Par-4 cDNA sequence.--

The paragraph beginning at page 34, line 13, has been amended as follows:

--Recruitment of endogenous components of the TNFR-1 signaling complex upon cell stimulation with TNFα has previously been demonstrated (Hsu *et al.*, Immunity 4:387-396 (1996); and McCarthy *et al.*, J. Biol. Chem., 273:16968-16975 (1998)). To examine the involvement of PS1 in TNFα-induced NF-κB activation, endogenous PS1 was immunoprecipitated at various time points from lysates of TNFα-treated and TNFα-untreated 293HEK cells. The immunoprecipitates were examined by immunoblot with an anti-RIP antibody. Briefly, subconfluent cultures of 293HEK cells were stimulated or not with 40ng/ml recombinant human TNFα (Calbiochem). Cells were then washed twice with ice cold PBS and lysed in 1 ml of lysis buffer (50 mM HEPES, 150 mM NaCl, 2 mM EDTA, 0.1% Nonidet P-40, 10 mM Na_3VO_4, and COMPLETE™ protease inhibitor mixture ([Complete™,]Boehringer Mannheim). Cells were lysed on ice for 15 minutes then centrifuged at 14,000 rpm for 20 minutes and the supernatants were collected. Lysates were then normalized such that equivalent

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amount of protein was present in each sample using the bicinchonic acid (BCA) method (Pierce). Lysates were pre-cleared for 2 hours with rabbit pre-immunization serum (5 μg) and 30 μl Protein-G agarose beads (Boehringer Mannheim). The lysates were then immunoprecipitated with 10 μg monoclonal anti-PS1 antibody. The immunoprecipitates were then washed five times in lysis buffer. Samples were resolved on 8% NuPage Tris-Glycine gels (Novex), transferred to PVDF membrane (Millipore) and subjected to Western blot analysis with an anti-RIP polyclonal antibody (Sigma).--

The paragraph beginning at page 37, line 18, has been amended as follows:

--Par-4 expression is enhanced in cells expressing PS1 mutations (PS1-FAD), and specifically inhibits the enzymatic activity of the aPKCs. As demonstrated in Figure 4C, Par-4 severely abrogated PS1 induced NF-κB activation. The aPKCs are key regulators of NF-κB activity and are negatively regulated by Par-4 (Diaz-Meco *et al.*, Cell 86:777-786 (1996)). Together with the evidence presented here that Par-4 impairs PS1-induced NF-κB activation (Figure 4C), this strongly suggests that increased expression of Par-4, following an apoptotic insult, could be sufficient to inhibit NF-κB survival-signaling, thereby sensitizing PS1-FAD expressing cells to the induction of apoptosis. To address this possibility, Par-4 mRNA levels in the stable PC12 cell lines were determined following exposure to an apoptotic insult. Par-4 mRNA levels were analyzed by quantitative real-time PCR. Briefly, total RNA was analyzed using an ABI P[rism]RISM™ 7700 Sequence Detection System (PE Applied Biosystems). RNA was extracted and purified from PC12 cell cultures using the RNAqueous kit (Ambion Inc.) according to manufacturer's instructions. Aliquots of RNA (2 μg) were reverse-transcribed using Multiscribe Reverse Transcriptase (PE Applied Biosystems). Sequence-specific primers and probes were designed using Primer Express software (PE Applied Biosystems). The primers and probes for 18S rRNA were: forward 5'-CGGCTACCACATCCAAGGAA-3' (SEQ ID NO: 11); reverse 5'-GCTGGAATTACCGCGGCT-3' (SEQ ID NO: 12); and probe 5' -6FAM-TGCTGGCACCAGACTTGCCCTC-TAMRA-3' (SEQ ID NO: 13). The primers and probes for Par-4 were: forward 5'-CCCAGATCCAGGAACCTCCT-3' (SEQ ID NO: 14); reverse 5'-TTTTGTATCTGCCTGGGACTGTT-3' (SEQ ID NO: 15) and probe 5'-6FAM-CCTGCCCCAGGACCCGTCG-TAMRA-3' (SEQ ID NO: 16). For RT-PCR analysis, 1 μl of

cDNA was used in a 25 µl reaction mixture in the presence of 200 nM of primers, 100 nM of probe and 0.625 unit of AmpliTaq Gold polymerase. Relative quantitation of Par-4 mRNA and 18S rRNA were calculated using the comparative threshold cycle number for each sample fitted to standard curve. Expression levels for the Par-4 mRNA in each sample were normalized to 18S rRNA.--

In the claims:

Claim 1 has been amended as follows:

Claim 1. (Twice amended) A method for identifying inhibitors of neuronal degeneration comprising:

(A) (1) cotransfecting eukaryotic host cells expressing a presenilin protein (PS), with a polynucleotide encoding a prostate apoptosis response-4 (Par-4) polypeptide, and an NF-κB dependent reporter construct, (2) exposing the cotransfected cells to a candidate molecule, (3) monitoring the ability of said candidate molecule to induce NF-κB activation, (4) comparing the level of NF-κB activation in the cells exposed to the candidate molecule to the level of NF-κB activation in at least one comparable control sample, and (5) identifying an inhibitor of neuronal degeneration when the level of NF-κB activation in the exposed cells is significantly greater than the level of NF-κB activation in the comparable control sample; or

(B) (1) transfecting eukaryotic host cells endogenously expressing prostate apoptosis response-4 (Par-4) polypeptide and a presenilin (PS) protein with nucleic acid encoding an NF-κB dependent reporter construct, (2) exposing the transfected cells to a candidate molecule, (3) monitoring the ability of said candidate molecule to induce NF-κB activation, (4) comparing the level of NF-κB activation in the cells exposed to the candidate molecule to the level of NF-κB activation in at least one comparable control sample and (5) identifying an inhibitor of neuronal degeneration when the level of NF-κB activation in the exposed cells is significantly greater than the level of NF-κB activation in the comparable control sample.--

FIGURE 15A

GAATTCCAGAAGGCAGGAACAGAGAAAGTAGAAGGAAAGTCTTATAAAAGAAAGAGAATAGGCC
AGGCACGGTGGCTCACGCCTCTAATCCCAGCATTTTGGGAGGCTGAGGCAGGTGGATCATGAGG
TCAGGAGTTCAAGACCAACCTGACCAACATGGTGAAGCCCCGTCTCTACTAAAAATACAAAAAT
TAACCAGGCGTGTGTGCCTGTAATCCCAGCTACTCAGGAGGCTGAGGCAGGAGAATCGCTTGAA
CCCGAAAGGTGAAGGTTGCTGTGAGCCTAGATCAGGCCACTGCACTCTGACCTGGGCGACAGAG
CGAGACTCCATGTCAAAGAAAAAGAAAGAGGATAAGAAAATTTCCTAACTGGAAGGCAGATAGC
TGATTAAAAGGGTCCACTGACTGCATAACATAATAATGATAAAAGACCAAATCAGAGCATATCT
TCAAGATATTTCAGAGGATCTAAGTAAGAAGATCCAAAAATTTTGAGACAGAAAATACAATGCA
ATCAGAATGCCACTGGTCTTCTAAACAGCAACTCTGGAAACTAGATGATAATAAAGCAATGCCT
TCAAAATTATGAAGGAAAATGCTTTCTAACCTAGAGTTCTATGCTCCACCAAACTATTAATCAA
GTATGAAGATAAATTTAAAACATTTTCCAATATGCAAGGTCTCTAAGAATGAGTTATACTATCT
TCAGAATATACTGAGGATATACTCTGCTAAAATGAAGGGGAGAAACAAAAAGAGAAAAGTATGC
AATTCAGGAAACAAGAAGTCTACAGAGAAAATGATTCTCAAGGTGTTAGAGGAGCATAATCCCA
GGATGACCACAAGCAACGAGCCTTAAAATCAGTCCAGATTAGGCCAGGTGCGGTGGCTCACACC
TGTAATCCCAGCACTTTGGGAGGCCAAAGCAGGCTGGTTGCCTGAGCTCAGAAGTTCGAGACCA
GTCTGGGCAACATGGTGAAACCCCCGTCTCTACTAAAATACAAAAAATTAGCTGGGCGTGGTGG
CATGTGCCTGTATTCCCAGCTACTCTGGAGGCTGATGCAGGAGAATTGCTTGAACCCAGGAGGC
GGAGGTTGCAGTGAGCCAAGACTGCGCCACTGCACTACAGCCTCACCAACAGAGCGAGACTCCG
TCTCCAAACAAACAAACAAAATCAATCCATATTAAAGCAGGGGATGGAGGGCTCCAGAACAGAT
GTTTCCAAAAAGAGAATAGAACTGATAGCTTACCCAATGTGATTAACGTCATTGAGAGGAGGAA
AATTTGAGTATATACTTGTGACTGGTATATAAAAAAATAAGCCGATGATTAAAGAAAAAAAAAG
AGGCAAGTTTTAACTGCAGAAAAATGGTAAAGACAAAAGGTATAGTTGTGCAACAAGGAAAAAC
AGTTGTAAAAAAAAAGAAATGCAATCATATACACCACATGACTCAGCTATGAACAGTATTTGTA
TAGTCATAATACTACGGGCGTGTAGGAGTATGAAAAGTATATGTGTGGCCGGGCATGGTGGCTC
ATGCCTGTAATCCCAGAACTTTGGGAGGCCGAGGCGGGTGGATCACGAGGTCAGGAGATCGAGA
TCATCCTGGCTAACACAGTGAAACCCCGTCTCTACTAAAAATGCAAAAAAAAAAAAAAAAAAAA
AAAAAAATTAGCCGGGCGTGGTGGCAGCCACCTGTAGTCCCAGCTACTCAGGAGGCTGAGGCAG
GAGAATGGCGTGAACCCGGGAGGCGGAGCTTGCAGTGAGCCGAGATCGCGCCACTGCACTCCAG
CCTGGGAGACAGAGCGAGACTCCATCTCAAAAAAAAAGAAAAAAAAAAGAAAAAGAAAAGAAAA
GTATATGTGTTATTAGTGTATTAGAGCTAAATCCTCTTCTATATCTAAAAATGGAAAAATCAAG
ATGTACAATAGCAGATATGCACATAAAAAATAAATATGAAGATCTCTATTAATGGAACCAGTTA
AAAAGTTCAAAGTTTTGGGTAGGGTTTTCAGAATGGATAAGGTAGAGAGGGGATTGCTGTTTTT
TGTTATAATCCTTGTAGAACTAAAGTATGTAATTTTTTTATCCTATGCACATATAATATTTTGA
TGTTAGAGGATGAATTGCATATGTTCCAGAAATACCTGCATTGAAGGCAAAATGGCTACTTCCC
AATACACTAGCTATCCATACATATAATAATACACTTCCTCAAAATCATTAAGACTAACATCTAG
GTTTCACTCTGACATATTTAAATGAATCTGTTTTTGTCAGCATTATCATCATATTTCATTTTAT
TATTAAGGGCAAGTGAGTCGCTAAAAATTGGTTATTTTAGGCTAACTCAGAGGTGCTCAACCGG
GGAAGAATTTTATCCCAGGGACCATGTGGCAATGTCACAATACAGGTGGGGGTTTCTTATTGGT
ATCTAATAGGTAGAAGCCAACGATGCTGCTAAACAACCTACAATGGGCAGGACAGCAAAGAATT
ATCCAGCCCCAAATGTAACAGTGCTGAGGTTGAGAAACCAAGCTCCAAGTCTTTGAGGATTATT
TCATCAGAACGCTATACATAAAGATTGATGATATGCAAACATCTTGCAATTTAGGACTGACTCA
GCTAAATACCTCGGTGCAATGTTGGAAGCAGTCTGGCTGTGAAATATATCTTCGGGAATATTGA
GAATGGTAAAGACAAAAGGTATAATAAATGATAATAATAACAAAACACAGAGCTTTGTACCTCA
ATAATCTCTTTCATCCATGGTTCCTAGGGCACTTTATAGACTAATAATACCTACTCTGGTACTC
ACATACCACCTTTTATCTAAGGACTGCAGGCACTTTCACAACACTCTCACGATGCAGGAAGTAT
TATTATCCCCATTTTATATGTAAGTAAACAGAGGCACAAAAGTTAAGCAACTTGCCCAAAGCCA

FIGURE 15B

ACAAGTCAGTAGCAGCCAAAATTCCTGACTCAGAACCTATTAACACTAAGAGAACTGGTCTAA
GCCATGCAGTGATAAATTTATGTGGGGTGTTATCCTAGTTCATTCAAAGTCTATCGTTTTTAGG
CTGATATTGTATATTCAATACCCCATCTGTTATAATTTCCTCTTCTCCCATACACTTCTTAGAG
ACCAAGGACTTTAAGCCCCTAGAAGGGACTATGTTTACTGAGTGCCTTCCTCGAATCAAGCACA
TTTTATGTGCAGTGTCAGTTCTTAAGACAGCTTAAATATAATGTAATTGGGAGGCTGAGAGCAG
GAGAATTGCTTGAACTCAGGAGGCGGAGGTTGCAGTGAGCTGAGATCCCGCCACTGCACTCCAG
CCTGGCGACAGAGCGAGACTCCGCCTCAAAAAAAAAAAAAAATGTAATTTTTGCTGATTTTATAG
TACAGAAAGCTGAGTACCAGATAATGTAAACATGCCCAAGATCTCTCAGCTAGCTGACTATTCC
CTCTTTCCACTATATCCTGCAGCCCTTCCAGGAGAAAAGTCCTCTGATAAGTTACAAAGCATAT
GAATGTGAATACGTTTAATGTCCCAGCCTCCCTTACTCTCCTTAAAACTCAGAAAACAAACTAA
TGAATATGTAATTGAGAAACTTCAGGTGGCACACTGGGGTTGGTACTAGCTTAGGTAAACAGCC
GCTCAGCCTTTTAGACCTATTCCCAACAAAAGCTTTTAATTTTCTAAGGATTTTTCCAGAGCTC
TCGCCATACGTTTCCCACAACAGCCAGACCAAAGACCAAAACTGTCTTTCCCTGAGAAATATAG
AGCATGTGAATCACTTTCTTCTGTTCCCAGTTCTGTGGCAGGCAAACACTGATTGCTCACTCAT
CATGTGCTACCTGGGCAAAACAGGAATATTAAGTAGGAAGAAAGGTTTATGTTAGGTAAGAGCG
TGACTTAGGGCTCTCCTACTTTTTTACAAAATGGAGACCTGGCATTTGTAGCCTCCCACAATGA
TGTGCCCTGACATTACTTGGATATAGAAAGGTCAGTCTTAGGTGCGTCAGTGACAGCCCACCCC
GCTCTGATCCAGAAATTTCAGATGACTTGCATCAGAGGATAAGCCTCTGGCATGTTAATAATGA
AAAAATAGAGACAATCACTGCCCCAGCTCATCTCAAATTAGCATCAGTGCAGCGTTAGTACTTT
GGTAGGGAGCTTTGCTGCTAAATTCATTCTCTGTAAAGAGGAGAGGCAGAGACAGGGTTAAGGG
GAAAACTCCAAGACTGGAATCGCCAATACAATAAACTGTCGAACTGAGTTTTTTCTCCCGCAAC
CCTAAGATACTAGTAAGTCCTTCCTCTTAGCCAACCCTTTTCACCAGGGCACCGCAGTTTTCTT
AGAAGGAGGGTGCTGGGTTTGTCTCAGGTCTTTCTATTCTCCTGCCCGCTGCCCTAGTACATCT
GAAAAGGGAGCAGCGACTAGGAAAAGAGACACGTGGGTATTTTCCCATCCTGTCTAGTCATTCC
CTGAATCATCACAAGTTATCGCACTTTTCCCCTTAGCCAGCAGCGTTCGAGACTTTCTCTCAAA
TAATACGGTCTTGTACTTAAAAGGAAGAGTGGTGGGAGAAGAGAGAGGCGGAGAAGACAAGCAA
GAAGGGCGTGGAGTGCCGTTCCCGCCCCGGAGTCGGAGGCGCCGGGAGGCCGGACGCCGCGAAG
CTGCTAGCCCAGGAATGTGCCGTCTAACTCGCAGGCCGCGGGCGGAGCGCGGCGGGCGCGCTGT
GGTCTGCGGCGGGAGCGGGGCAGAGGACGGCTGGCGCAGGGCAGGCTGCAGCGGCGGGCCGGAC
GCGACGCCGCGCACCTGAGCGCCGGGGGCGGGGCGTCAGCGGCCACGACCCTTCCCACCGCGCG
CCGCGCCCCTCGCGCGCCGCCTCGGCCTTTTCCGCTCGTGCTTCGGCGCCGCTCGGCTCCCTTC
CCGCCCCTGGCTCCCTCCCTCCCTCCCTCCCTCCTTCTTCTCCCTCCCTCCTGTCCTGGGATTG
CCTGGAGCTCCGCACCGCGAGTTTGCCGCGGCACTTTCCGCGCGGCGGAAGAGCGCGCGCCAGC
TTCGGCACACCTGGGAGCCGGATCCCAGCCCTACGCCTCGTCCCCTACAAGCTCCTCCAAGGTA
AGGCGCTCGCTCACACCCGGTCCTTTCCACGCTCGGCGGGACAGCTGGGTCCCCGCCTCCTCTG
CGAACCGGCTAGGAGCTCCGCGCCTCGCC**TTGGGAGTGGGGTTGTAGCTGACGGGGACCTCGGA**
CCGGCGGTGGCTAGAGCGCGGAGCAGGCGATACGACGAGCCGACAGGTGGCGGGTCTAGCCCTA
GTATCTCGACCGCCGCCGGCGCGGACCTTGGTGGGGATGGGGCGGGCGGGCCGACTTGGGGGTG
GGGTCAGTCCTCTCTCCTCCCTTCTAGGGGCGGCGATCGTCGGGGTCCGTACTGTAGGTGCGTG
GGAGAAACTTTGCAGGGTGGGGACCCGGCGGCTGCTGGCCGGTAGTGACTGGTGGGCGCGCTCG
AGGACTCCAAGGGGCGCAGCCCGGGGGCAGACCCTTGGGTCGGGCGGGGATCTTACGCTTCCCT
TACCCGCCCCCTTTTGTCTTTCACCTCAGCCCCGCCGGCTGCTGTGGGAGCGGCGGCCGTCCCT
CTCCTGGAGGTCGTCTCCTGGCATCCTCGGGGCCGCAGGAAGGAAGAGGAGGCAGCGGCCGGAG
CCCTGGTGGGCGGCCTGAGGTGAGAGCCCGACCGGCCCCTTTGGGAATATGGCGACCGGTGGCT
ACCGGACCAGCAGCGGCCTCGGCGGCAGCACCACAGACTTCCTGGAGGAGTGGAAGGCGAAACG
CGAGAAG**ATGCGCGCCAAGCAGAACCCCCCGGGCCCGGCCCCCCCGGGAGGGGGCAGCAGCGAC**
GCCGCTGGGAAGCCCCCCGCGGGGGCTCTGGGCACCCCGGCGGCCGC